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Abstract. Diffusion tensor MRI (DT-MRI) allows the in vivo assessment of the abnormalities of white matter in multiple sclerosis (MS). DT-MRI is complementary to conventional MRI sequences where such abnormalities are often not visible. Most studies have shown differences of mean diffusivity (MD) and fractional anisotropy (FA) between patients and controls in MS lesions (MSL) and normal appearing white matter (NAWM) based on histogram analyses. However, the majority of these studies are based on histogram analysis, i.e. local information of DT-MRI is lost, and moreover a number of those studies were not conclusive, partly explained by methodological issues, because these tensor indices vary within the brain, which is likely to make such global, histogram-based analyses, fail. Here we propose a new framework to compare these indices between MSL and NAWM and between two populations (patients and controls). First, MSL are manually delineated in MS patients. The mid-sagittal plane is then automatically computed, allowing to define a contralateral region of interest (ROI) in NAWM for each MSL. This allows the local comparison of DTI indices in anatomically similar regions in each MS patient. Second, each MS patient is linearly registered to each control subject, and the same left-right comparison between MSL and contralateral NAWM is then performed in controls. The results (ANOVA with multiple comparisons procedure) show that 1) FA values are lower in MSL than in contralateral NAWM in MS patients ($p < 0.05$) but not in controls, 2) FA values are lower in MS patients (MSL and contralateral NAWM) compared to controls ($p < 0.05$), 3) MD values are not different between MSL/contralateral NAWM in MS patients and controls. We also show that combining different preprocessing methods (3 estimation methods and 3 distortion correction methods) has little impact on such results. Nevertheless, our fully automated approach is superior to manual or semi-automated DT-MRI analyses regarding the robustness of the results (reproducibility and accuracy).

1 Introduction

Since its description in 1986 by Le Bihan *et al.* [1], diffusion-weighted MRI has gained increasing attention in the neuroimaging community. DW-MRI allows to measure non-invasively the water molecular self-diffusion in biologic tissues. The movement of water molecules is strongly related to the underlying anatomical structure and allows a biophysical characterisation of the tissue organisation. This information is especially relevant for fibres where the water molecular movement is orientation-dependent due to microscopic barriers, such as muscles, ligaments, tendons, or fibre bundles composing the white matter of the central nervous system (CNS). DW-MRI allows the study of the normal and pathological brain, as it provides a unique insight into the microscopic physiological phenomena occurring in living tissues. A particularly simple way to exploit DW-MRI data has been introduced by Basser *et al.* [2] in 1994, termed diffusion-tensor magnetic resonance imaging (DT-MRI). In MS, DT-MRI findings correlated with qualitative characteristics of MSL using conventional MRI sequences, but in contrast to conventional MRI, DT-MRI conveys at the same time biophysical and quantitative properties. In patients with MS, important and significant DW-MRI findings were reported with regard to focal (MSL) and diffuse (normal appearing white matter (NAWM) and normal appearing grey matter (NAGM)) pathology both in the brain and the spinal cord. Studies were performed with histogram analysis of the diffusion characteristics (ADC/FA/MD) in the whole brain or large parts of it [3–6]. Analysis of semi-automatically delineated regions of interest (ROI) were performed both in MSL and the NAWM [7–16]. Overall, in MSL, but also in the NAWM and NAGM, increased values of MD and decreased values of FA/RA were reported. Even if DT-MRI in MS conveys more detailed information about tissue damage than conventional MRI studies it should be kept in mind that DT-MRI shows a good sensitivity to detect diffusion abnormalities and has the potential to exhibit de- or re- myelinisation effect . On the other hand DW-MRI lacks specificity to distinguish between changes in membrane permeability, tissue integrity, gliosis, inflammation or axonal loss. Heterogeneous results of diffusion imaging in MS lesions have been explained by lesion heterogeneity, basically in terms of lesion age, degree of tissue loss and presence or absence of active inflammation on conventional MRI (*i.e.* Gd-enhancement) [7–13, 17]. Correlations between diffusion measures and clinical scales have been rather disappointing, and their correlation is at best moderate [5,6,13,17–21]. Furthermore, DW-MRI studies in MS suggest that focal MD or FA changes do not correlate with brain atrophy measurements [22, 23], and moderate correlations were found with ROI histogram analysis [4].

In this paper, we propose to compare three automated methods of diffusion tensor estimation, and also three automated image distortion corrections for the processing of MR Diffusion Tensor Images (DTI) in patients with multiple sclerosis (MS). Here we propose automated tools for the exact comparison of DTI invariants (fractional anisotropy (FA) and mean diffusivity (MD)) between lesions and their contralateral regions of interest (ROI) in the normal appearing white matter (NAWM).

2 Methods

A lot of different methods for the estimation of tensors have been proposed in the past few years, but none has been evaluated in a pathological context. As of today most of the studies involving MS and DTI were conducted using standard least squares (LS) estimation of the tensors. This classical method has been shown to have more variation in both trace and orientation of the tensors than the weighted least squares (wLS) or constrained non linear least squares (CNLS) methods [24]. Another very important pre-processing is the correction of eddy current distortion [25], and is often either not performed or done using a very simple model. In this paper we compare the effects of distortion correction using linear, polynomial second order and polynomial third order transformations, and no distortion correction on DTI invariants of MSL and their contralateral counterparts. The contralateral ROIs are automatically computed using the mid-sagittal plane as a reference [26]. The comparison was performed using ANOVA and multiple comparison procedure in two main groups : 1) MSL and 2) contralateral ROI as well as for each of the combination of pre-processing (12 groups), resulting in 24 entries in our multiple comparisons procedure.

2.1 Diffusion tensor estimation

In order to exploit the information included in diffusion-weighted MRI (DW-MRI) a model of the diffusion is required. The first proposed model that can provide information on the fiber orientation is the tensor model of the diffusion. This model is the simplest available one for the diffusion in order to include fiber orientation and is the most often used model in the clinical context. A tensor is mathematically represented by a 3×3 matrix, which is symmetric and definite positive (SDP), this reflects the physical meaning that the diffusion in a direction can neither be negative nor null. The computation of a tensor is based on the Stejskal-Tanner equation, $S_i = S_0 e^{-bD_i}$, which links each image point, voxel, of a diffusion unweighted image S_0 to the spatially corresponding voxels in the diffusion-weighted images S_i with the diffusion coefficient D_i dependant on the acquisition parameter b. The previous equation is written for each diffusion-weighted image with gradient g_i using tensors as $S_i = S_0 e^{-b g_i^T \mathbf{D} g_i^T}$ where $\mathbf{D}$ is a tensor. The diffusion tensor being a symmetric matrix only six coefficients need to be computed. This is the reason for the acquisition of a number of diffusion weighted images equal at least to six.

In a paper reviewing the tensor estimation techniques Koay et al. [27] showed that this estimation can result in quite different tensors in terms of orientation and shape. The most interesting result of this paper is that the constrained non linear least square has been shown to have the lower relative error in estimating the MD and FA than other methods [24,27]. In most DTI and MS related papers the estimation if performed using simple linear least squares (LS) estimation or weighted least squares (wLS). We propose to compare these two methods

(LS,wLS) and CNLS (the best one according to Koay *et al.*) in order to measure the impact of such techniques.

2.2 Correction of distortions

DT-MRI consists in acquiring one diffusion-unweighted image and several diffusion-weighted images with non-collinear direction-encoding gradients. The tensor summarising the diffusion information is then computed on a voxel-by-voxel basis. Echo Planar Imaging (EPI) is generally used for the acquisition of DW-MRI data. This fast technique reduces the effects due to the subject's motion, but is especially sensitive to eddy currents. These induce geometrical distortions that cause misregistration of the MRI data and thus inaccuracy of the reconstructed tensor. We use different models for the transformation due to the distortions:

- An Affine model (12 parameters)
- Two global polynomial models with polynomials of order 2 and 3 (30 and 60 parameters).

2.3 Mid-Sagittal Plane (MSP) computation

We propose a method for the automated computation of the mid-sagittal plane (MSP) of the brain in diffusion tensor MR images. We estimate this plane as the one that best superposes the two hemispheres of the brain by reflection symmetry [28]. This is done via the automated minimization of a correlation-type global criterion over the tensor image which computes the plane parameters. The MSL are then flipped with respect to the MSP, giving contralateral ROI located in the NAWM.

3 Experiments

The data are acquired using axial (2 mm slice thickness) DW-MRIs on a 3T (Philips) with 15 directions. The database was constituted with five patients with MS and five control subjects (sex- and age-matched).

Conventional DT-MRI tools were applied for the computation of DTI invariants (FA and MD maps). The diffusion tensors were calculated using the LS, wLS and CNLS methods and four methods for the corrections of distortions were applied to the DW-MRI (no correction, affine and the two polynomial models). For controls, the mask of lesions from the MS patients were automatically aligned with the images of the controls, using a linear registration method [25].

The lesion mask and contralateral mask of lesion were then used to extract paired-data on the FA and MD maps for each MS patient and control. An analysis of variance (ANOVA) combined with a multiple comparison procedure is then applied to the FA and MD data from each ROI. The ANOVA is fed with voxel data intensity, grouped by ROI: 1) MSL, 2) contralateral MSL ROI, 3) control ROI, 4) control contralateral ROI and by preprocessing. The Figure

1 and 2 show the multiple comparisons procedure output. These Figures has the controls and MS patients displayed as two groups, for this two groups the pre-processing are ordered as follow:

- correction of distortion with affine model
  - tensor estimation with WLS for the lesion and contralateral ROI
  - tensor estimation with LS for the lesion and contralateral ROI
  - tensor estimation with CNLS for the lesion and contralateral ROI
- correction of distortion with polynomial second order model
  - tensor estimation with WLS for the lesion and contralateral ROI
  - tensor estimation with LS for the lesion and contralateral ROI
  - tensor estimation with CNLS for the lesion and contralateral ROI
- correction of distortion with polynomial third order model
  - tensor estimation with WLS for the lesion and contralateral ROI
  - tensor estimation with LS for the lesion and contralateral ROI
  - tensor estimation with CNLS for the lesion and contralateral ROI
- no correction of distortions
  - tensor estimation with WLS for the lesion and contralateral ROI
  - tensor estimation with LS for the lesion and contralateral ROI
  - tensor estimation with CNLS for the lesion and contralateral ROI

In our experiments, whatever processing was applied, three statistically different groups appear on the FA (Fig. 1):

- MSL in MS patients
- Contralateral of MSL in MS patients
- Controls (both "lesion" and contralateral ROI).

On the FA maps of controls, a slight difference appears depending on the applied processing. On average, this is mainly due to the higher anisotropy in the controls data. The differences in the tensor estimation techniques are clearer in regions of high anisotropy, which is reflected by our experiments. The correction of distortions does not seem to yield specifically different results. For the MD, no statistically different results appear (Fig. 1) but a small variation still exists on two of the preprocessings.

4 Results

In MS patients a statistical difference between lesions and their contralateral counterparts was found for the FA (but not for the MD), irrespective of the automated image processing methods used. In controls, no statistical difference between ROI associated with MS patient lesions and contralateral ROI was found.

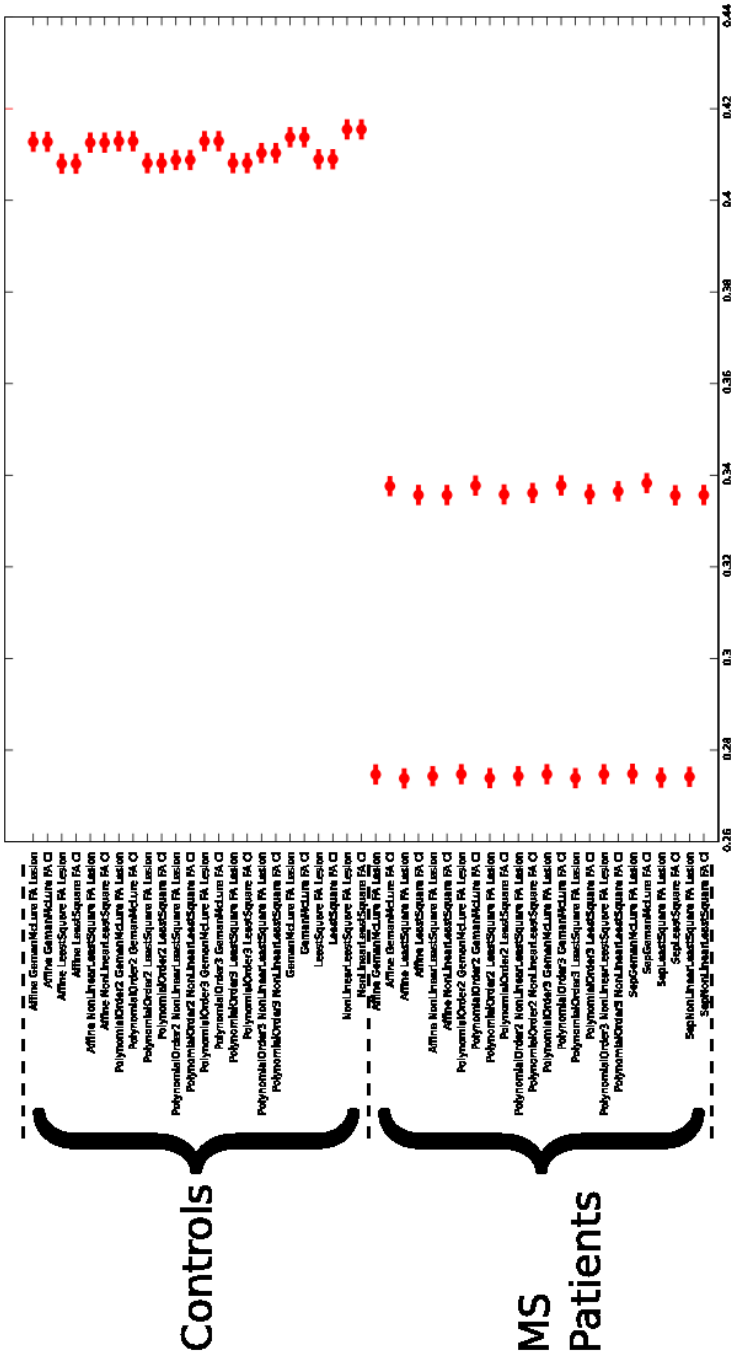

Fig. 1. Multiple Comparison procedure results on FA Maps

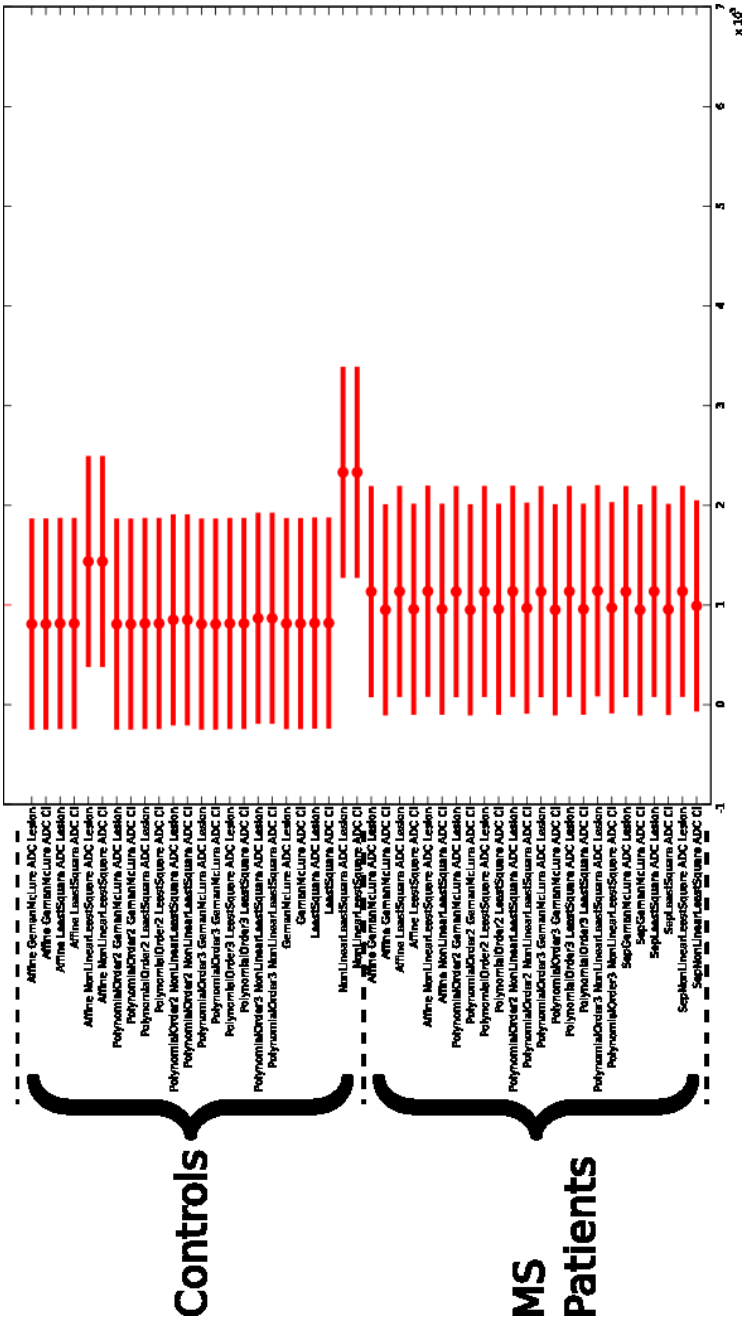

Fig. 2. Multiple Comparison procedure results on MD Maps

5 Conclusion

In comparison with widely used manual or semi-automated DTI analysis methodology, in this pilot study with MS patients and age- and sex-matched controls, we show with our automated approach using the mid-sagittal plane as a reference that we were able to replicate results from the literature. Automated image analysis approaches, however, have the advantage being more accurate, reproducible and robust. A statistical difference between MSL and their contra lateral ROI is confirmed as shown in the literature, which does not exists for controls. A statistical difference is present when comparing the three tissues classes from MS patients and controls: 1) MSL ROI, 2) contralateral ROI MSL and 3) controls ROI. Even if the pre processing seems to impact little on statistical differences of the DTI measures in healthy volunteers and MS patients our fully automated approach is superior to manual or semi-automated DT-MRI analyses regarding the robustness of the results (reproducibility and accuracy).

References

1. Le Bihan, D. *et al.*: MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. Radiology **161**(2) (November 1986) 401–7
2. Basser, P. *et al.*: Estimation of the effective self-diffusion tensor from the NMR spin echo. Journal of Magnetic Resonance **B**(103) (1994) 247–254
3. Rovaris, M. *et al.*: Diffusion MRI in multiple sclerosis. Neurology **65**(10) (November 2005) 1526–1532
4. Wilson, M. *et al.*: Quantitative diffusion weighted magnetic resonance imaging, cerebral atrophy, and disability in multiple sclerosis. J Neurol Neurosurg Psychiatry **70** (march 2001) 318–322
5. Ciccarelli, O. *et al.*: Investigation of MS normal-appearing brain using diffusion tensor MRI with clinical correlations. Neurology **56**(7) (April 2001) 926–933
6. Nusbaum, A.O. *et al.*: Whole-brain diffusion MR histograms differ between MS subtypes. Neurology **54**(7) (April 2000) 1421–1427
7. Bammer, R. *et al.*: Magnetic resonance diffusion tensor imaging for characterizing diffuse and focal white matter abnormalities in multiple sclerosis. Magnetic Resonance in Medicine **44** (2000) 583–591
8. Droogan, A.G. *et al.*: Comparison of multiple sclerosis clinical subgroups using navigated spin echo diffusion-weighted imaging. Magn Reson Imaging **17** (June 1999) 653–661
9. Filippi, M. *et al.*: A quantitative study of water diffusion in multiple sclerosis lesions and normal-appearing white matter using echo-planar imaging. Arch Neurol **57**(7) (July 2000) 1017–1021
10. Roychowdhury, S. *et al.*: Multiple Sclerosis: Comparison of Trace Apparent Diffusion Coefficients with MR Enhancement Pattern of Lesions. AJNR Am J Neuroradiol **21**(5) (May 2000) 869–874
11. Werring, D.J. *et al.*: Diffusion tensor imaging of lesions and normal-appearing white matter in multiple sclerosis. Neurology **52** (May 1999) 1626–1632

12. Castriota-Scanderbeg, A. *et al.*: Coefficient Dav Is More Sensitive Than Fractional Anisotropy in Monitoring Progression of Irreversible Tissue Damage in Focal Non-active Multiple Sclerosis Lesions. AJNR Am J Neuroradiol **24**(4) (April 2003) 663–670
13. Filippi, M. *et al.*: Diffusion tensor magnetic resonance imaging in multiple sclerosis. Neurology **56**(3) (February 2001) 304–311
14. Nusbaum, A.O. *et al.*: Regional and Global Changes in Cerebral Diffusion with Normal Aging. AJNR Am J Neuroradiol **22** (January 2001) 136–142
15. Ranjeva, J.P. *et al.*: MRI/MRS of corpus callosum in patients with clinically isolated syndrome suggestive of multiple sclerosis. Mult Scler **9**(6) (December 2003) 554–565
16. Cassol, E. *et al.*: Diffusion tensor imaging in multiple sclerosis: a tool for monitoring changes in normal-appearing white matter. Mult Scler **10**(2) (April 2004) 188–196
17. Scanderbeg, A.C. *et al.*: Demyelinating Plaques in Relapsing-remitting and Secondary-progressive Multiple Sclerosis: Assessment with Diffusion MR Imaging. AJNR Am J Neuroradiol **21**(5) (May 2000) 862–868
18. Cercignani, M. *et al.*: Intra-voxel and inter-voxel coherence in patients with multiple sclerosis assessed using diffusion tensor MRI. Journal of Neurology **249**(7) (July 2002) 875–883
19. Cercignani, M. *et al.*: Mean Diffusivity and Fractional Anisotropy Histograms of Patients with Multiple Sclerosis. AJNR Am J Neuroradiol **22**(5) (May 2001) 952–958
20. Bozzali, M. *et al.*: Quantification of Brain Gray Matter Damage in Different MS Phenotypes by Use of Diffusion Tensor MR Imaging. AJNR Am J Neuroradiol **23**(6) (June 2002) 985–988
21. Rovaris, M. *et al.*: Assessment of normal-appearing white and gray matter in patients with primary progressive multiple sclerosis: a diffusion-tensor magnetic resonance imaging study. Arch Neurol **59**(9) (September 2002) 1406–1412
22. Iannucci, G. *et al.*: Correlation of Multiple Sclerosis Measures Derived from T2-Weighted, T1-Weighted, Magnetization Transfer, and Diffusion Tensor MR Imaging. AJNR Am J Neuroradiol **22**(8) (September 2001) 1462–1467
23. Stefano, N.D. *et al.*: MR correlates of cerebral atrophy in patients with multiple sclerosis. J Neurol **249** (August 2002) 1072–1077
24. Koay, C.G., Basser, P.J.: Analytically exact correction scheme for signal extraction from noisy magnitude MR signals. J Magn Reson **179**(2) (April 2006) 317–322
25. Wiest-Daesslé, N. *et al.*: Evaluation of a new optimisation algorithm for rigid registration of MRI data. In: SPIE Medical Imaging 2007: Image Processing. (2007) to be published.
26. Prima, S., Wiest-Daesslé, N.: Computation of the Mid-Sagittal Plane in Diffusion Tensor MR Brain Images. In: SPIE Medical Imaging 2007: Image Processing. (2007) to be published.
27. Koay, C.G. *et al.*: A unifying theoretical and algorithmic framework for least squares methods of estimation in diffusion tensor imaging. J Magn Reson **182**(1) (September 2006) 115–125
28. Wiest-Daesslé, N. *et al.*: Validation of a new optimisation algorithm for registration tasks in medical imaging. In: IEEE International Symposium on Biomedical Imaging 2007, Washington DC, USA (April 2007)